

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**



(19)

Europäisches Patentamt

European Patent Office

Office européen des brevets



(11)

EP 0 411 941 B1

(12)

EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention
of the grant of the patent:
17.07.1996 Bulletin 1996/29

(51) Int. Cl.⁶: C07F 9/38, C07F 9/6524

(21) Application number: 90308524.9

(22) Date of filing: 02.08.1990

(54) Process for purifying aminomethylenephosphonic acids

Verfahren zur Reinigung von Aminomethylenphosphonsäuren

Procédé de purification d'acides aminométhylène phosphoniques

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IT LI LU NL SE

(74) Representative: Raynor, John et al
W.H. Beck, Greener & Co
7 Stone Buildings
Lincoln's Inn
London WC2A 3SZ (GB)

(30) Priority: 04.08.1989 US 389441

(56) References cited:
EP-A- 0 225 409

(43) Date of publication of application:
06.02.1991 Bulletin 1991/06

- K. SCHWETLICK ET AL 'Organikum Organisch-Chemisches Grundpraktikum' 1969, VEB DEUTSCHER VERLAG DER WISSENSCHAFTEN, BERLIN
- CHEMICAL ABSTRACTS, vol. 107, no. 25, 21 December 1987, Columbus, Ohio, US; abstract no. 236855M, S.A. PISAREVA ET AL: 'Synthesis and complexformation properties of ...' page 803 ;column 1 ;
- CHEMICAL ABSTRACTS, vol. 97, no. 17, 25 October 1982, Columbus, Ohio, US; abstract no. 145013U, page 703 ;column 1 ;

(73) Proprietor: THE DOW CHEMICAL COMPANY
Midland, Michigan 48640 (US)

(72) Inventors:

- Garlich, Joseph R.
Lake Jackson, Texas 77566 (US)
- Masterson, Tipton T.
Lake Jackson, Texas 77566 (US)
- Simon, Jaime
Angleton, Texas 77515 (US)

EP 0 411 941 B1

Note: Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

Description

Many organic aminophosphonic acids and their salts are well known compounds, especially for their use in chelating metal ions. Some of these organic aminophosphonic acids and their salts are used as threshold inhibitors. U. S. Patent 2,599,807 discloses some of these compounds and describes methods for their preparation. An example of the preparation given in this patent discloses heating an aqueous solution of ethylenediamine and then adding to it a solution of the sodium salt of chloromethylenephosphonic acid and an excess of a base, e.g. Na_2CO_3 , to maintain a pH of from 10 to 11.5. After adding at least a stoichiometric amount of the phosphonating reagent, i.e. sufficient to form the completely phosphonated amine salt [i.e., the sodium salt of ethylenediaminetetra(methylenephosphonic acid), (known as NaEDTMP)], the solution is refluxed at its boiling point for from one to five hours. The solution is then cooled and neutralized to a pH of from 6 to 7 and evaporated to dryness to recover the desired ethylenediaminetetra(methylenephosphonic acid), [known as EDTMP].

Another process which makes the symmetrical ethylenediaminedi(methylenephosphonic acid) in good yield involves treating an aqueous solution of two molar portions of aminomethylenephosphonic acid with one molar portion of an alkylene dihalide at an elevated temperature for a time sufficient to insure complete reaction. This reaction can be accomplished in a few hours under reflux in 50 percent ethanol.

In another patent, U. S. Patent 3,738,987, the reaction to form the aminophosphonic acid is begun by introducing PCl_3 into water to form phosphorous acid and hydrochloric acid (HCl). The polyamine is then introduced into this acid solution. It is preferred to have a 5 to 10 percent excess of the PCl_3 . When the amine is added, the reaction medium is at a temperature of about 38 to 50°C. When all the amine has been added, the temperature is raised to about 93 to 104°C and an aqueous solution of formaldehyde is sparged into the reaction mixture, during which time the temperature is maintained at that level and for several hours thereafter and finally cooled.

In a more recent published patent, Japanese No. 55-150501, it is disclosed that much higher yields of the desired product are obtained by adding the amine to a mixture of phosphorous and hydrochloric acids in which the H_3PO_3 is in excess with respect to the amine, preferably from about 4.3 to 5.5 moles of the acid per mole of amine. Concentrated HCl is used, preferably about 2.2 moles HCl per mole of amine. Too much acid will tend to increase the amount of water in the system, which is undesirable. No additional water is added to the reaction mixture, which is apparently the reason for the improved yields, since all the other processes use water and dilute acids.

It has recently been discovered that certain of the methylenephosphonated amines are useful for imaging

and other radiopharmaceutical uses when complexed as chelates with radioactive metals. Use of the compounds for such purposes requires the highest purity materials.

It has now been found that, even when using the preferred processes of the known art, impurities are formed, e.g. the N-methylated species in which an amine hydrogen is replaced by a methyl group rather than by the methylenephosphonic acid moiety.

While a process to obtain high purity aminophosphonic acids is known, a process to make an even higher purity of such products is the subject of this invention. The present process involves certain procedures for recrystallization to obtain the desired high purity products.

Surprisingly, a crystallization process has now been found which produces certain very high purity (99+ percent) aminomethylenephosphonic acids, e.g. ethylenediaminetetra(methylenephosphonic acid), [known as EDTMP], and 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetra(methylenephosphonic acid), [known as DOTMP]. EDTMP and DOTMP may each be complexed to various metals to form pharmaceutical products (see, for example, U.S. Patents 4,898,724 and 4,882,142, respectively). Other aminophosphonic acids are not easily purified in this manner because of their greater solubility in water at low pH values. For example, diethylenetriaminepenta(methylenephosphonic acid) [known as DTPMP] and nitrilotri(methylenephosphonic acid) [known as NTMP] cannot be purified by the present process.

The present process of recrystallization is accomplished by the steps of:

- (a) dissolving the aminophosphonic acid in an aqueous base;
- (b) adding the solution from step (a) to an acid solution, optionally maintained at an elevated temperature, to reprecipitate the aminophosphonic acid;
- (c) optionally heating the solution for a period of time sufficient to assure that precipitation of the aminophosphonic acid has begun;
- (d) filtering the aminophosphonic acid crystals; and
- (e) washing the crystals with water.

The first step (a) dissolves the aminophosphonic acid in an aqueous base, preferably ammonium hydroxide, which is followed by acidifying the solution with an acid, preferably a mineral acid, to a pH within the range of from 0 to 4 (step b). Acidification with the acid may be carried out either by adding the solution to the acid, or adding the acid to the solution. The acidic solution may then be refluxed, preferably at a temperature of from 35 to 105°C, more preferably from 70 to 105°C, for a period of time, preferably of from 0.5 to 3 hours, more preferably from 0.5 to 1 hour (step c). The solution can then optionally be cooled, preferably to a temperature of from about ambient temperature to about 95°C, more preferably from 25 to 45°C, and allowed to remain at that temperature for a period of time to permit the desired precipita-

tion, preferably for a period of from 1 to 24 hours, more preferably from 12 to 24 hours. The precipitated, i.e. recrystallized, aminophosphonic acid is then filtered, preferably at the lower temperature, to obtain the desired purified crystals (step d) which are then washed thoroughly with water to remove any solution which might contain undesired impurities (step e). The process is repeated one or more times, if the desired purity has not been attained. A product containing 0.1 percent or less impurities can be obtained by the above process.

Of course, the number of times the recrystallization process of this invention is repeated will depend on the purity desired in the final product and also on the purity of the starting aminomethylenephosphonic acid.

It has now been determined that, in the case of EDTMP, if the reaction medium is filtered prior to substantial cooling, the resulting EDTMP product has a higher purity than if the reaction medium is cooled before filtering. Best results are obtained if the filtration is done while the reaction medium is at reflux temperature. It is believed that this is because the impurities are more soluble in the hot solution.

The following example illustrates the method of preparation which results in the purest EDTMP product. Additional examples below show the recrystallization process to provide the products which can be used for pharmaceutical purposes.

Example 1. Preferred Preparation of EDTMP

A 5-L 3-neck flask equipped with a mechanical stirrer fitted with a Teflon™ paddle was charged with phosphorous acid (755 g) to which was added concentrated (conc.) HCl (1.2 L). After vigorous stirring, the phosphorous acid dissolved, causing the solution temperature to drop to 0°C. To this cold solution was added ethylenediaminedihydrochloride (271 g) and heat was applied with vigorous stirring. At about 60°C, a large volume of HCl gas was given off, which was conveniently recovered with a water gas trap. At about 88°C all the ethylenediaminedihydrochloride was dissolved and heating was continued to 100°C (reflux). Once the reaction had reached 100°C, a 37% aqueous solution of formaldehyde (902 mL) was added dropwise via a peristaltic pump over a 22-24 hour period (rate was 0.65 mL/min). After an additional four hour reflux time, the boiling suspension was vacuum filtered (1.5 L sintered glass filter) and washed with two 300 mL portions of water. This solid was air dried and 607 g (70% yield) of EDTMP, m.p. 216-217 decomposition (d) (lit. m.p. 214 d) is recovered. H-1 and P-31 NMR analyses of this sample indicated the impurities were at a level of less than 1%.

Example 2. Purification of EDTMP

A quantity of 1050 g of the EDTMP prepared by the procedure of Example 1 was added to 1050 mL water in a 2-L round-bottomed flask and stirred with a mechanical stirrer fitted with a Teflon™ paddle. Concentrated NH₄OH

(325 mL) was added in 25-mL increments over a one hour period. After all the NH₄OH was added, almost all the EDTMP had gone into solution. The small amount that was not soluble was removed by vacuum filtration. The clear filtrate was then poured with stirring into 2100 mL of refluxing 3M hydrochloric acid in a 5-L round-bottomed flask equipped with a heating mantle and thermometer (set at 100°C). The resulting stirred solution was clear and the temperature had dropped to 68°C. Stirring was continued and after six minutes the temperature had risen to 72°C and a slight precipitate was visible. Within 16 minutes, with continued stirring, the temperature was 87°C and the precipitate was heavy. After 20 minutes, the temperature was again at reflux (100°C). After 30 minutes at reflux temperature, the thermometer setting was lowered to 43°C. After stirring for 21 hours at 43°C, the suspension was vacuum filtered through a sintered glass funnel while still warm. Water (500 mL) was used to transfer the heavy solid from the flask to the filter funnel. The filter cake thus obtained was washed with three 500-mL portions of water and air dried overnight to give 984.8 g of EDTMP, m.p. 214-215°C. A P-31 NMR spectrum of this sample indicated about 0.6% impurity. The EDTMP used as starting material had impurity levels of about 1%.

Example 3. Purification of EDTMP

A sample of EDTMP prepared in Example 2 (970 g, 0.6% impurity) was dissolved in 970 mL of water in a 2-L round-bottomed flask by the addition of 323 mL of concentrated NH₄OH in 25-mL portions. After all solids were dissolved, the solution was poured with stirring into 1940 mL of refluxing 3N aqueous HCl. The temperature dropped to 74°C and after seven minutes, had risen to 82°C with a faint precipitate visible. After 30 minutes, more precipitate had formed and the temperature had reached 100°C. The suspension was left at reflux for an additional hour after which the temperature was lowered to 43°C and stirred for an additional 13 hours. At the end of this time, the suspension was vacuum filtered using 450 mL of water to transfer, washed with three 400-mL portions of water and air dried to give 920.4 g of EDTMP, m.p. 214-215°C. A P-31 NMR spectrum of this sample indicated about 0.4% impurity level.

The following Examples illustrate the purification of EDTMP from different sources.

Example 4. Purification of EDTMP

The product of Example 3 (0.4% impurity, 900 g) was dissolved in 900 mL of water in a 2-L round-bottomed flask by the addition of 300 mL conc. NH₄OH over a 20-minute period. The solution was poured with stirring into 1800 mL of refluxing 3N aqueous HCl. The temperature of the resulting solution dropped to 72°C and after five minutes of stirring with heat it had risen to 78°C with some precipitate present. Within 30 minutes the temperature was back to 100°C and was left there for one hour

after which the temperature was lowered to 43°C. After stirring overnight (17.5 hours) at 43°C, the heavy precipitate was vacuum filtered using 400 mL of water to transfer, washed with three 400-mL portions of water and air dried to give 805.62 g of EDTMP, m.p. 215-217°C. A high field P-31 NMR spectrum indicated an impurity level of around 0.1% for this sample of EDTMP.

Example 5. Purification of EDTMP

A sample (50 g, 115 mmoles) of EDTMP containing 5.81% impurities by P-31 NMR was dissolved in 50 mL of water by the addition of 13.5 mL (193 mmoles) conc. NH₄OH in small portions over a period of 15 minutes. This solution of the ammonium salt of EDTMP was then poured with stirring into 100 mL (300 mmoles) of refluxing 3N HCl. The temperature, which dropped to 73°C, was brought back to reflux (100°C) with application of additional heat and vigorous stirring. The EDTMP began precipitating from solution almost immediately and continued to precipitate with continued stirring and heating. The solution was maintained at reflux for one hour after which the temperature was lowered to 43°C and the suspension allowed to stir for 21 hours, after which the heavy white precipitate was vacuum filtered at that temperature, using 25 mL of water to transfer and three additional 25 mL portions of water to wash the precipitate. The precipitate was air dried to give 41.4 g (95 mmole, 83% yield) of EDTMP. Analysis of this precipitate by P-31 NMR indicated the impurity level had dropped to 2.05%.

Example 6. Purification of EDTMP

A sample (50 g, 115 mmoles) of EDTMP containing 5.81% impurities by P-31 NMR was dissolved in 50 mL of water by the addition of 13 mL (186 mmoles) conc. NH₄OH in small portions over a period of 15 minutes. This solution of the ammonium salt of EDTMP was then poured with stirring into 100 mL (300 mmoles) of refluxing 3N HCl. The temperature, which dropped to 72°C, was brought back to reflux (100°C) with application of additional heat and vigorous stirring. The EDTMP began precipitating from solution almost immediately, and continued to precipitate with continued stirring and heating. The solution was maintained at reflux with stirring for 22 hours, after which the heavy white precipitate was vacuum filtered at that temperature, using 25 mL of water to transfer and three additional 25 mL portions of water to wash the precipitate. The precipitate was air dried to give 34.3 g (79 mmoles, 69% yield) of EDTMP. Analysis of this precipitate by P-31 NMR indicated the impurity level had dropped to 1.45%.

Example 7. Purification of EDTMP

A sample (50 g, 115 mmoles) of EDTMP containing 5.81% impurities by P-31 NMR was dissolved in 50mL of water by the addition of 13 mL (186 mmoles) conc. NH₄OH in small portions over a period of 15 minutes.

This solution of the ammonium salt of EDTMP was then poured with stirring into 100 mL (300 mmoles) of refluxing 3N HCl. The temperature, which dropped to 72°C, was brought back to reflux (100°C) with application of additional heat and vigorous stirring. The EDTMP began precipitating from solution almost immediately, and continued to precipitate with continued stirring and heating. The solution was maintained at reflux for one hour, after which the temperature was lowered to 70°C and the suspension allowed to stir for 21 hours, after which the heavy white precipitate was vacuum filtered at that temperature, using 25 mL of water to transfer and three additional 25 mL portions of water to wash the precipitate. The precipitate was air dried to give 41.4 g (95 mmole, 83% yield) of EDTMP. Analysis of this precipitate by P-31 NMR indicated the impurity level had dropped to 2.05%.

Example 8. Purification of EDTMP

A sample (50 g, 115 mmoles) of EDTMP containing 5.81% impurities by P-31 NMR was dissolved in 50 mL of water by the addition of 13 mL (186 mmoles) conc. NH₄OH in small portions over a period of 15 minutes. This solution of the ammonium salt of EDTMP was then poured with stirring into 100 mL (300 mmoles) of refluxing 3N HCl. The temperature, which dropped to 72°C, was brought back to reflux (100°C) with application of additional heat and vigorous stirring. The EDTMP began precipitating from solution almost immediately and continued to precipitate with continued stirring and heating. The solution was maintained at reflux for one hour after which the heat source was removed and the suspension allowed to stir at room temperature for 21 hours after which the heavy white precipitate was vacuum filtered at that temperature, using 25 mL of water to transfer and three additional 25 mL portions of water to wash the precipitate. The precipitate was air dried to give 41.2 g (94 mmole, 82% yield) of EDTMP. Analysis of this precipitate by P-31 NMR indicated the impurity level had dropped to 2.11%.

Example 9. Purification of EDTMP

A sample (50 g, 115 mmole) of EDTMP (DEQUEST™ 2041, a commercial sample from the Monsanto Company for a series of aminophosphonic acid chelating agents) containing 3.65% impurities by P-31 NMR was dissolved in 50 mL of water by the addition of 16 mL (229 mmoles) conc. NH₄OH in small portions over a period of 15 minutes. This solution of the ammonium salt of EDTMP was then poured with stirring into 100 mL (300 mmoles) of refluxing 3N HCl. The temperature, which dropped to 72°C, was brought back to reflux (100°C) with application of additional heat and vigorous stirring. The EDTMP began precipitating from solution almost immediately and continued to precipitate with continued stirring and heating. The solution was maintained at reflux for one hour after which the temperature was lowered to 43°C and the suspension allowed to stir

for 21 hours after which the heavy white precipitate was vacuum filtered at that temperature, using 25 mL of water to transfer and three additional 25 mL portions of water to wash the precipitate. The precipitate was air dried to give 44.3 g (102 mmole, 89% yield) of EDTMP. Analysis of this precipitate by P-31 NMR indicated the impurity level had dropped to 1.85%.

Example 10. Purification of EDTMP

A sample (50 g, 115 mmoles) of EDTMP containing 5.81% impurities by P-31 NMR was dissolved in 50 mL of water by the addition of 16 mL (229 mmoles) conc. NH₄OH in small portions over a period of 15 minutes. This solution of the ammonium salt of EDTMP was then poured with stirring into 100 mL (300 mmoles) of refluxing 3N HCl. The temperature, which dropped to 72°C, was allowed to cool to 43°C with continued vigorous stirring. The EDTMP began precipitating from solution almost immediately and continued to precipitate while the suspension was allowed to stir for 21 hours at 43°C. The heavy white precipitate was then vacuum filtered at that temperature, using 25 mL of water to transfer and three additional 25 mL portions of water to wash the precipitate. The precipitate was air dried to give 42.7 g (98 mmole, 85% yield) of EDTMP. Analysis of this precipitate by P-31 NMR indicated the impurity level had dropped to 2.95%.

Examples A and B following are comparative.

Example A. Comparative of DTPMP

A 5 g (8.73 mmoles) sample of diethylenetriaminepenta(methylenephosphonic acid), DTPMP, was dissolved in 4 mL of water by the addition of 1.526 mL (21.82 mmoles) conc. NH₄OH in small portions over a period of 15 minutes. This solution of the ammonium salt of DTPMP was then poured with stirring into 9.15 mL (27.45 mmoles) of refluxing 3N HCl. The temperature, which dropped to 76°C, was brought back to reflux (100°C) with application of additional heat and vigorous stirring. The solution was maintained at reflux for one hour after which the temperature was lowered to 43°C and the suspension allowed to stir for 91 hours. Even at the end of this lengthy period of stirring, no precipitate had formed. The solution was allowed to remain at room temperature without stirring for an additional 8 days with periodic observation. No precipitate had formed at the end of this time.

Example B. Comparative of NTMP

A sample of nitrilotri(methylenephosphonic acid), NTMP, (3 g, 10 mmoles) was dissolved in 4.32 mL of water by the addition of 1.049 mL (15.0 mmoles) conc. NH₄OH in small portions over a period of 15 minutes. This solution of the ammonium salt of NTMP was then poured with stirring into 6.3 mL (18.9 mmoles) of refluxing 3N HCl. The temperature, which dropped to 83°C,

was brought back to reflux (100°C) with application of additional heat and vigorous stirring. The solution was maintained at reflux for one hour after which the temperature was lowered to 43°C and allowed to stir at that temperature for 89 hours. Even at the end of this lengthy period of stirring, no precipitate had formed. The solution was allowed to remain at room temperature without stirring for an additional 8 days with periodic observation. No precipitate had formed at the end of this time.

10

Example 11. Preparation of DOTMP

Into a 100 mL, three-necked, round-bottomed flask, equipped with a thermometer, reflux condenser and heating mantle, was placed 3.48 g (20.2 mmoles) of 1,4,7,10-tetraazacyclododecane (a commercial product obtained from Parish Chemical Company, Orem, Utah) and 14 mL water. To this solution was added 17.2 mL of conc. HCl and 7.2 g of H₃PO₄ (87.7 mmoles) and the solution was heated to 105°C. The refluxing solution was stirred vigorously while 13 g (160.2 mmoles) of formaldehyde (37% aq. soln.) was added over a period of one hour. The refluxing solution was stirred an additional two hours. The heat was then removed and the solution allowed to cool to room temperature and stand for 62.5 hours. The reaction solution was concentrated by heating at 40°C *in vacuo* to a reddish brown semi-solid. A 30-mL portion of water was added which produced a suspension. This suspension was then poured into 400 mL of acetone with vigorous stirring. The resulting off-white precipitate was vacuum filtered and dried overnight to give 10.69 g (97% yield) of DOTMP.

Example 12. Purification of DOTMP

35

A 2.0 g (3.65 mmoles) sample of DOTMP from Example 11 was dissolved in 2 mL of water by the addition of 700 µL conc. NH₄OH in 100 µL portions to give a solution having a pH of 2-3. This solution was then added all at once to 4.5 mL of 3N HCl (13.5 mmoles), mixed well, and allowed to stand. Within one hour, small nearly square crystals had begun to form on the sides of the glass below the surface of the liquid. The crystal growth was allowed to continue and the crystals were gently bumped off the vessel walls, filtered, washed with four 3-mL portions of water and air dried to constant weight to give 1.19 g (60% yield) of white crystalline solid m.p. 270 (d)°C.

The DOTMP signal in the decoupled P-31 NMR spectrum of the starting material represented 78.1% of the total phosphorous signals present while that of the product obtained after the base/acid recrystallization, represented 94.7% of the total phosphorous present.

55

Example 13. Preparation of DOTMP

Into a 250-mL three-necked, round-bottomed flask, fitted with a thermometer, temperature controller, addition funnel and stirring bar and attached to a reflux con-

denser was placed 6.96 g (0.04 mole) 1,4,7,10-tetraazacyclododecane (a commercial product obtained from Parish Chemical Company, Orem, Utah). To this was added 14.5 g (1.77 moles) phosphorous acid, 30 mL deionized water and 28 mL (0.336 mole) conc. HCl. After the solution had been brought to reflux temperature (105°C), aqueous (37%) formaldehyde (26.0 g, 0.32 mole) was introduced into the flask through the addition funnel during a 30 to 40-minute period. The solution was heated and stirred for three more hours at reflux and then permitted to cool to ambient temperature.

The reaction solution was then transferred to a 500 mL round bottomed flask and attached to a roto-evaporator apparatus. The solution was evaporated to an amber, viscous semi-solid, the temperature never exceeding 40°C in the heating bath. To the viscous material was added about 300 mL HPLC grade acetone, producing a light brown, sticky, viscous oil which was then dissolved in 22 mL of water and added slowly with vigorous stirring to 1 L of acetone. The acetone was decanted and the light colored oil dried under vacuum to give 16.6 g (76% yield) of crude DOTMP. A portion (13.1 g) of the crude DOTMP was dissolved in 39.3 g deionized water, treated with a seed crystal and allowed to stand overnight. The resulting precipitate was vacuum filtered, washed with cold water and dried under vacuum to give 4.75 g (36% yield) of DOTMP.

Example 14. Purification of DOTMP

A quantity (3.0 g, 5.47 mmoles) of the DOTMP prepared in Example 13 was recrystallized by dissolving it in 3 mL of water by the addition of 2.2 mL (31.5 mmoles) of conc. NH₄OH. This solution was added with stirring to 2.4 mL (28.8 mmoles) of conc. HCl at which time a white solid precipitated. This precipitate was vacuum filtered and dried to give 2.42 g (81% yield) of DOTMP, m.p. 280 (d)°C.

The DOTMP signal in the decoupled P-31 NMR spectrum of the starting material represented 97.2% of the total phosphorous signals present. The DOTMP signal in the decoupled 31-P NMR spectrum of the product after the base/acid recrystallization, represented 98.2% of the total phosphorous signals present.

Example 15. Preparation of DOTMP

Into a 250-mL beaker containing 85.77 g (.871 mole) conc. HCl was added (57.11 g, 0.696 mole) solid phosphorous acid and dissolved with stirring. A 250 mL three-necked, round-bottomed flask was loaded with 1,4,7,10-tetraazacyclododecane (10.00 g, 0.58 mole) and attached to a reflux condenser. This apparatus was placed on a heater/stirrer and fitted with a thermometer which controlled an infra-red lamp through a temperature controller. The acid solution was carefully added to the reaction flask containing 1,4,7,10-tetraazacyclododecane.

The reaction mix, which had become a white slurry, was brought to reflux temperature (about 105°C). Aqueous 37% formaldehyde solution (94.12 g, 1.16 moles) was added all at once to the reaction mix. The slurry immediately turned to a clear solution. The reaction was continued at reflux with constant stirring for approximately five hours. The reaction solution was cooled and 188 mL transferred to a one liter Erlenmeyer flask and diluted with 470 mL of 0.1M hydrochloric acid solution (1 to 3.5 dilution). The solution was seeded with a few grains of DOTMP and placed in the refrigerator overnight. The resulting white solid precipitate (1.35 g) was collected 17 hours later by filtration on a medium glass fritted funnel. The filtrate was transferred from the filter flask back into the one liter Erlenmeyer, seeded again with a few grains of DOTMP, and placed in the refrigerator overnight. The next day the white precipitate was filtered (2.70 g) and the filtrate concentrated under vacuum to 80 mL. This filtrate was then diluted with 200 mL of water, seeded as above and allowed to stand in a refrigerator for 72 hours, after which the white solid was filtered and dried to give 8.85 g (28% yield) of DOTMP.

Example 16. Purification of DOTMP

In the reactor of Example 15 a 50 mL three-necked flask was loaded with 15.6 mL of 3N HCl solution (46.8 mmoles) and placed on a heater/stirrer. This solution was taken up to reflux temperature (about 103°C). A separate solution was made by placing DOTMP (8.00 g, 14.6 mmoles), prepared in Example 15, into a 50 mL beaker and dissolving it by adding 8.00 g HPLC grade water and (2.52 mL, 36.0 mmoles) of concentrated (14.3M) ammonium hydroxide.

The DOTMP/NH₃ solution was added all at once with constant stirring to the refluxing 3N HCl solution. The temperature dropped to about 75°C and was quickly brought back to reflux and maintained there for about one hour. The temperature was lowered to 43°C and maintained there for a period of 21 hours. This slurry was then filtered through a glass medium filter funnel, transferring it with about 4 mL water and washing the filter cake additionally with about 4 mL of water. The filter cake was air dried to give 6.79 g (85% yield) of a fine, white solid. Analysis showed that the co-products were reduced from 6.85% in the original DOTMP sample of Example 15 to 3.11% in this sample.

Example 17. Purification of DOTMP

Into a 50-mL three-necked flask, fitted with a thermometer and water jacketed condenser, was introduced a 3N HCl solution (13.25 mL, 39.76 mmoles). This apparatus was placed on a heater/stirrer and heated to reflux.

A separate solution of DOTMP was prepared by adding the DOTMP (6.79 g, 12.38 mmoles), prepared in Example 12, to a 50 mL beaker and dissolving it by adding 6.8 g of water and 2.14 mL (30.59 mmoles) of concentrated ammonium hydroxide. This solution was fil-

tered through a paper filter to remove trace solids; then added all at once to the refluxing hydrochloric acid solution prepared above. The resulting white suspension was heated for one hour at reflux and then the temperature was lowered to 43°C. After allowing the suspension to stir at this temperature for a total of about 21 hours the white solid was filtered through a fine glass fritted funnel, washed with about 8 mL of deionized water, then allowed to air dry. A total of 6.14 g (90% yield) of DOTMP was thus recovered as a fine white solid. Analysis by P-31 NMR showed an increase in purity from 96.89% for the DOTMP used as starting material to 98.37% for the DOTMP product recovered.

Example 18. Purification of DOTMP

A 50 mL three-necked, round bottomed flask was loaded with 12.0 g (36.0 mmoles) of 3N hydrochloric acid solution. A stir bar was added and the HCl solution was brought up to reflux temperature with constant stirring.

A 50 mL beaker was loaded with 6.14 g (11.2 mmoles) of DOTMP prepared in Example 17. An equal weight of deionized water was added (341.1 mmoles) and the DOTMP was brought into solution through the addition of 1.94 mL (27.7 mmoles) of concentrated ammonium hydroxide. This solution was filtered through a paper filter to remove undissolved solids, then added all at once with vigorous stirring to the refluxing hydrochloric acid solution. A white precipitate formed immediately from the addition of the two water-clear solutions. The suspension was heated to reflux and allowed to stir for about one (1) hour at this temperature. The temperature of the flask was then lowered to about 43°C and allowed to stir at this temperature for a total of about 21 hours.

The white solid was filtered at this temperature, washed with 8 mL of water and air dried to give 5.90 g (87% yield) of purified DOTMP. Analysis by P-31 NMR indicated greater than 99% purity of DOTMP had been achieved.

Example 19. Purification of DOTMP

The 1.35 g sample and the 2.7 sample of DOTMP prepared in Example 15 were combined and ground to a fine powder. A P-31 NMR analysis of this sample indicated 6.40% non-DOTMP phosphorous-containing by-products were present. A 1.00 g (1.82 mmoles) sample of this DOTMP was added to a 3-dram vial along with a 1.00 g portion of water and a stir bar. This slurry was stirred while adding concentrated ammonium hydroxide (315 μ L, 4.5 mmoles) in small portions (42 μ L) until completely dissolved.

A 4-dram vial was loaded with 1.95 mL of 3N HCl solution (5.85 mmoles) and equipped with a stirring bar and reflux condenser. This solution was brought to reflux temperature using a mineral oil bath. The DOTMP solution from above was added to the refluxing HCl solution with stirring dropping the temperature to 75°C. This solu-

tion was again brought to reflux and held for one hour with constant stirring. The temperature was then lowered to 43°C and held there with constant stirring for a total of 21 hours. The white precipitate was then filtered and washed with 4 portions of 0.5 mL of cold water. The 0.72 g (72% yield) of DOTMP thus purified showed only 2.28% phosphorous containing by-products when analyzed by P-31 NMR.

Example 20. Purification of DOTMP

The recrystallization of Example 19 was repeated except that after the one hour reflux period the solid was filtered while hot, washed with hot water, and dried to give 0.84 g (84% yield) of DOTMP. This material was analyzed by P-31 NMR and found to contain only 1.74% phosphorous containing by-products as compared to 6.40% present in the starting DOTMP.

Example C. Comparative for EDTMP

In the apparatus of Example 13 was placed 7.51g (0.125 mole) ethylenediamine, 47.3g (0.5 mole) phosphorous acid, 59 mL conc. HCl (0.737 mole) and 80 mL water. The solution was heated to reflux with stirring and treated with 16.6g (0.5 mole) paraformaldehyde, added in small portions over a one hour period. The solution was then refluxed an additional 2.5 hours and allowed to cool to room temperature overnight. The resulting white solid EDTMP was then vacuum filtered and washed with two 50-mL portions of water. This procedure gave 32.27g (60% yield) EDTMP. Analysis of this sample by P-31 NMR indicated a 6.4% level of by-products present.

Example 21.

The procedure of Comparative Example C above was repeated using half the above amounts. After all the paraformaldehyde had been added, a portion of the reaction solution was maintained at 90-97°C overnight after which a voluminous white precipitate had appeared. The suspension was filtered while still hot and washed with two 40-mL portions of hot 3N HCl. The solid thus isolated was air-dried to give 5.25 g EDTMP, containing only 1.4% by-product level.

Claims

1. A process for purifying ethylenediaminetetra(methyleneephosphonic acid) or 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetra(methyleneephosphonic acid) which comprises the steps of:
 - (a) dissolving the aminophosphonic acid in an aqueous base;
 - (b) acidifying the solution from step (a) with an acid to reprecipitate the aminophosphonic acid;
 - (c) filtering the aminophosphonic acid crystals; and

- (d) washing the crystals with water.
2. A process as claimed in Claim 1, wherein the aqueous base in step (a) is ammonium hydroxide.
- 5
3. A process as claimed in Claim 1 or Claim 2, wherein the acid in step (b) is a solution of a mineral acid.
- 10
4. A process as claimed in Claim 3, wherein the mineral acid is hydrochloric acid.
- 15
5. A process as claimed in any one of the preceding claims, wherein the pH of the mixture after the addition of the acid solution from step (a) to the acid is from 0 to 4.
- 20
6. A process as claimed in any one of the preceding claims, wherein after addition of the solution from step (a) to the acid, the solution is heated to assist purification of the aminophosphonic acid.
- 25
7. A process as claimed in Claim 6, wherein the said heating is carried out for from 0.5 to 3 hours.
8. A process as claimed in Claim 7, wherein the heating period is from 0.5 to 1 hour.
- 30
9. A process as claimed in any one of Claims 6 to 8, wherein the said heating is carried out at a temperature of from 35 to 105°C.
10. A process as claimed in Claim 9, wherein the temperature is from 70 to 105°C.
- 35
11. A process as claimed in any one of Claims 6 to 10, including a step of cooling the solution before the filtration step (c).
12. A process as claimed in Claim 11, wherein the solution is cooled to a temperature of some ambient to 95°C.
- 40
13. A process as claimed in Claim 11 or Claim 12, wherein the solution is cooled to a temperature of from 25 to 45°C.
- 45
14. A process as claimed in any one of Claims 11 to 13, wherein the solution is cooled for from 1 to 24 hours.
15. A process as claimed in Claim 14, wherein the solution is cooled for from 12 to 24 hours.
- 50
16. A process as claimed in any one of the preceding claims, wherein the acid used for acidification of the solution of step (a) is at an elevated temperature.
- 55
17. A process as claimed in any one of the preceding claims, wherein step (a) to (c) inclusive are repeated at least once.
18. A process for preparing ethylenediaminetetra(methylenephosphonic acid) which comprises reacting ethylenediamine, phosphorous acid, hydrochloric acid and formaldehyde or paraformaldehyde and heating the reaction medium to reflux temperature, characterised in that the product is filtered from the reaction medium prior to cooling.
19. A process as claimed in Claim 18, wherein the filtration is accomplished while the reaction medium is at reflux temperature.
20. A process as claimed in Claim 18, wherein the ethylenediamine is in the form of a hydrochloride.

Patentansprüche

1. Verfahren zum Reinigen von Ethylenediamintetra(methylenephosphonsäure) oder 1,4,7,10-Tetraazacyclododecan-1,4,7,10-tetra(methylenephosphonsäure), welches die Schritte umfaßt:
 - (a) Auflösen der Aminophosphonsäure in einer wäßrigen Base;
 - (b) Ansäuern der Lösung aus Schritt (a) mit einer Säure, um die Aminophosphonsäure erneut zu präzipitieren;
 - (c) Filtrieren der Aminophosphonsäurekristalle; und
 - (d) Waschen der Kristalle mit Wasser.
2. Verfahren nach Anspruch 1, worin die wäßrige Base in Schritt (a) Ammoniumhydroxid ist.
3. Verfahren nach Anspruch 1 oder Anspruch 2, worin die Säure in Schritt (b) eine Lösung einer Mineralsäure ist.
4. Verfahren nach Anspruch 3, worin die Mineralsäure Salzsäure ist.
5. Verfahren nach einem der vorhergehenden Ansprüche, worin der pH-Wert des Gemisches nach der Zugabe der sauren Lösung aus Schritt (a) zu der Säure von 0 bis 4 beträgt.
6. Verfahren nach einem der vorhergehenden Ansprüche, worin nach Zugabe der Lösung aus Schritt (a) zu der Säure die Lösung erwärmt wird, um die Reinigung der Aminophosphonsäure zu unterstützen.
7. Verfahren nach Anspruch 6, worin das Erwärmen während 0,5 bis 3 Stunden durchgeführt wird.
8. Verfahren nach Anspruch 7, worin der Erwärmungszeitraum von 0,5 bis 1 Stund beträgt.

9. Verfahren nach einem der Ansprüche 6 bis 8, worin das Erwärmen bei einer Temperatur von 35 bis 105°C ausgeführt wird.
10. Verfahren nach Anspruch 9, worin die Temperatur von 70 bis 105°C beträgt. 5
11. Verfahren nach einem der Ansprüche 6 bis 10, umfassend einen Schritt, worin die Lösung vor dem Filtrationsschritt (c) gekühlt wird.
12. Verfahren nach Anspruch 11, worin die Lösung auf eine Temperatur von etwa Raumtemperatur bis 95°C gekühlt wird.
13. Verfahren nach Anspruch 11 oder Anspruch 12, worin die Lösung auf eine Temperatur von 25 bis 45°C gekühlt wird.
14. Verfahren nach einem der Ansprüche 11 bis 13, worin die Lösung während 1 bis 24 Stunden gekühlt wird.
15. Verfahren nach Anspruch 14, worin die Lösung von 12 bis 24 Stunden gekühlt wird.
16. Verfahren nach einem der vorhergehenden Ansprüche, worin die zur Ansäuerung der Lösung aus Schritt (a) verwendete Säure eine erhöhte Temperatur hat.
17. Verfahren nach einem der vorhergehenden Ansprüche, worin Schritte (a) bis einschließlich (c) mindestens einmal wiederholt werden.
18. Verfahren zum Herstellen von Ethyleniamintetra(methylenephosphorsäure), welches das Umsetzen von Ethyleniamin, Phosphorsäure, Salzsäure und Formaldehyd oder Paraformaldehyd und das Erwärmen des Reaktionsmediums auf Rückflußtemperatur umfaßt, dadurch gekennzeichnet, daß das Produkt vor Kühlung vom Reaktionsmedium abfiltriert wird.
19. Verfahren nach Anspruch 18, worin die Filtration ausgeführt wird während das Reaktionsmedium Rückflußtemperatur hat.
20. Verfahren nach Anspruch 18, worin das Ethyleniamin in der Form eines Hydrochlorids vorliegt.
- Revendications**
1. Procédé qui consiste à purifier l'acide éthylénemaminetétraméthylénephosphonique ou acide 1,4,7,10-tétraazacyclododécane-1,4,7,10-tétra(méthylèneosphosphorique) et qui comprend les étapes de :
- (a) dissolution de l'acide aminophosphonique dans une base en solution aqueuse ;
 (b) acidification de la solution provenant d l'étape (a) avec un acide afin de reprécipiter l'acide aminophosphonique ;
 (c) filtration des cristaux d'acide aminophosphonique ; et
 (d) lavage des cristaux avec de l'eau.
10. Procédé conforme à la revendication 1, dans lequel la base en solution aqueuse de l'étape (a) est l'hydroxyde d'ammonium.
15. Procédé conforme à la revendication 1 ou 2, dans lequel l'acide de l'étape (b) est une solution d'un acide minéral.
20. Procédé conforme à la revendication 3, dans lequel l'acide minéral est l'acide chlorhydrique.
25. Procédé conforme à l'une quelconque des précédentes revendications, dans lequel le pH du mélange après l'addition de la solution d'acide provenant de l'étape (a) à l'acide vaut de 0 à 4;
30. Procédé conforme à l'une quelconque des précédentes revendications, dans lequel après l'addition de la solution provenant de l'étape (a) à l'acide, on chauffe la solution pour faciliter la purification de l'acide aminophosphonique.
35. Procédé conforme à la revendication 6, dans lequel on effectue ledit chauffage pendant une durée de 0,5 à 3 heures.
40. Procédé conforme à la revendication 7, dans lequel la durée de chauffage est de 0,5 à 1 heure.
45. Procédé conforme à l'une quelconque des revendications 6 à 8, dans lequel on effectue ledit chauffage à une température de 35 à 105°C.
50. Procédé conforme à la revendication 9, dans lequel la température vaut de 70 à 105°C.
55. Procédé conforme à l'une quelconque des revendications 6 à 10, comprenant une étape de refroidissement de la solution avant l'étape de filtration (c).
12. Procédé conforme à la revendication 11, dans lequel on refroidit la solution à une température qui se situe dans l'intervalle allant de la température ambiante à 95°C.
13. Procédé conforme à la revendication 11 ou 12, dans lequel on refroidit la solution à une température qui se situe dans l'intervalle allant de 25 à 45°C.

14. Procédé conforme à l'une quelconque des revendications 11 à 13, dans lequel on refroidit la solution pendant 1 à 24 heures.
15. Procédé conforme à la revendication 14, dans lequel on refroidit la solution pendant 12 à 24 heures. 5
16. Procédé conforme à l'une quelconque des précédentes revendications, dans lequel l'acide utilisé pour l'acidification de la solution de l'étape (a) se trouve à une température élevée. 10
17. Procédé conforme à l'une quelconque des précédentes revendications, dans lequel on répète les étapes de (a) à (c) incluse au moins une fois. 15
18. Procédé de préparation de l'acide éthylenediamine-tétra(méthylénephosphonique) qui comprend le fait de faire réagir l'éthylenediamine, l'acide phosphoreux, l'acide chlorhydrique et le formaldéhyde ou le paraformaldéhyde, et le fait de chauffer le milieu réactionnel jusqu'à une température de reflux, caractérisé en ce qu'on filtre le produit du milieu réactionnel avant de refroidir. 20
- 25
19. Procédé conforme à la revendication 18, dans lequel on réalise la filtration tandis que le milieu réactionnel se trouve à une température de reflux.
20. Procédé conforme à la revendication 18, dans lequel l'éthylenediamine est sous la forme d'un chlorhydrate. 30

35

40

45

50

55

10